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Intravenous Lidocaine Versus Fentanyl on Pain Scale and Interleukin-6 Levels After Curettage: A Double-Blind Randomized Controlled Trial

Restian Rudy O[1]*, Rth. Supraptomo[1], Purwoko[1], Septian Adi Permana[1], Fitri Hapsari Dewi[1]
[1]Anesthesiology and Intensive Therapy Specialist Education Program, Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia
***Corresponding author:** Restian Rudy O., E-mail: **restianrudy@yahoo.com**

ABSTRACT

Background: Dilation and curettage is a common obstetric procedure, and postoperative pain accompanied by raised interleukin-6 (IL-6) has been linked to postoperative complications. Fentanyl is widely used as an intraoperative analgesic, whereas intravenous lidocaine has analgesic and anti-inflammatory properties. This study compared the two drugs on postoperative pain and IL-6 in obstetric patients undergoing curettage.

Methods: A double-blind randomized controlled trial was conducted at the Comprehensive Emergency Obstetric and Neonatal Care Unit of Dr. Moewardi General Hospital, Surakarta, from August to October 2023. Thirty-two patients (ASA I–II, aged 20–40 years) received lidocaine 1.5 mg/kg (n = 16) or fentanyl 1 µg/kg (n = 16) intravenously after induction of general anesthesia. Pain was measured with the Numeric Rating Scale (NRS) at 4 and 12 hours postoperatively, and IL-6 was measured by ELISA before surgery and 4 hours afterward. Groups were compared with the Mann–Whitney test and within-group changes with the Wilcoxon test.

Results: NRS scores decreased significantly in both groups between 4 and 12 hours (p < .001) and did not differ between groups at 4 hours (p = .515) or 12 hours (p = .361). IL-6 increased significantly in both groups (p < .001), with no between-group difference before surgery (p = .867) or 4 hours afterward (p = .793).

Conclusion: Intravenous lidocaine and fentanyl showed no detectable difference in postoperative pain scores or IL-6 response after curettage. Because the sample was small and possibly underpowered, and no equivalence or non-inferiority margin was prespecified, non-inferiority cannot be concluded; larger adequately powered trials are needed.

Keywords: Pain Scale; Interleukin-6; Fentanyl; Lidocaine; Curettage

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INTRODUCTION

Dilation and curettage is among the most common invasive gynecological procedures. It is used for elective termination of pregnancy and for the management of missed, incomplete, or inevitable abortion in the first trimester (Cooper & Menefee, 2023), and it is also a common way of establishing the cause of abnormal uterine bleeding and treating it (Butwick et al., 2017). Anesthesia for the procedure may be general or regional (Akhondzadeh et al., 2019; Krishnamohan et al., 2016). Because bleeding is common in this type of surgery, maintaining hemodynamic stability during anesthesia is essential (Mostafa et al., 2021).

Postoperative complications are a heavy burden in surgery. Although several predictors have been identified, higher perioperative levels of inflammatory markers have been associated with a higher incidence of postoperative complications. Curettage causes pain, although its intensity differs between individuals (Karnina & Ismah, 2021), and most patients report moderate to severe pain after surgery, possibly related to under- or overdosing of opioids during the operation (Meijer et al., 2020). Pain is a frequent problem among women after surgery and is accompanied by rising interleukin-6 (IL-6) levels, and higher IL-6 has been associated with postoperative complications (Isbul et al., 2023; Neff et al., 2021). IL-6 also takes part in pain mechanisms and in hypersensitivity related to inflammation and neuropathy, interacting not only with immune and glial cells but also with neurons along the pain pathway (Isbul et al., 2023; Sebba, 2021).

IL-6 is a pro-inflammatory and immunoregulatory cytokine that is important in neutrophil activation and in mediating oxidative responses; it is a 25-kDa secreted glycoprotein of 184 amino acids (Uciechowski & Dempke, 2020). It is produced in response to tissue damage and contributes to host defense by stimulating the acute-phase response, hematopoiesis, and immune reactions, and its expression is tightly controlled because dysregulated synthesis has pathological effects in chronic inflammation and autoimmunity (Tanaka et al., 2014). IL-6 induces hepatic synthesis of acute-phase proteins such as C-reactive protein, serum amyloid A, fibrinogen, and hepcidin (Gulhar et al., 2023). Monocytes and macrophages are its main producers, although many other cell types can also produce it, and IL-6 is widely measured because it stays detectable in blood for a relatively long time and rapid assays are available; its concentration has been used as a marker of the severity of disease or injury (Gubernatorova et al., 2018). IL-6 is also widely expressed in the female reproductive tract and gestational tissues, where it regulates embryo implantation, placental development, and immune adaptation to pregnancy, and raised IL-6 is common in unexplained infertility, recurrent miscarriage, preeclampsia, and preterm labor (Pantos et al., 2022; Prins et al., 2012). IL-6 is therefore of particular interest in obstetric populations.

Pain is the product of three events along the nociceptive pathway, namely transduction, transmission, and modulation, and acute pain arises mainly from nociception, in which tissue damage activates and sensitizes nociceptors (Aribawa et al., 2019; Yam et al., 2018). Perioperative analgesia must therefore act on both nociception and the inflammatory response that accompanies tissue injury.

An ideal anesthetic provides calm and rapid anesthesia, allows immediate recovery after the procedure, has a wide safety margin, and causes no adverse effects (Dewi & Suprianto, 2019). The choice of drug in general anesthesia must therefore be considered carefully (Imani et al., 2021). Two agents that can be given are fentanyl and lidocaine. Fentanyl is a potent opioid used to control pain, reduce the dose of other agents, and maintain hemodynamic stability; a small dose given before induction can reduce the incidence and intensity of pain (Luong, 2020; Mulier, 2016). Lidocaine is an amide-type local anesthetic with analgesic, antihyperalgesic, and anti-inflammatory effects, although the exact mechanism of its anti-inflammatory action remains unclear (Lee & Schraag, 2022).

Earlier studies have examined fentanyl and lidocaine in relation to pain and IL-6. In rats with perioperative fentanyl-induced hyperalgesia, local infiltration with 0.2 mL of 0.5% levobupivacaine, given before or after incision, significantly lowered IL-6 compared with controls (Chang et al., 2018). In another study, fentanyl and morphine consumption did not differ during and after surgery, yet a 1.6-point increase in postoperative pain score was observed (Meijer et al., 2020). Bolus and continuous intravenous lidocaine effectively reduced pain

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intensity but did not significantly lower plasma IL-6 (Sardi et al., 2022). In a trial of preoperative lidocaine 1.5 mg/kg intravenously before hysteroscopy under general anesthesia, the incidence of pain in the post-anesthesia care unit was significantly lower than in controls (27.3% vs. 68.2%, $p < .001$; Lee et al., 2020).

Fentanyl and lidocaine each have advantages. Fentanyl is increasingly used for perioperative analgesia and stable hemodynamics, but it is a popular intraoperative analgesic that has been linked to opioid tolerance and opioid-induced hyperalgesia (Rupniewska-Ladyko & Malec-Milewska, 2019). Lidocaine is an effective modality for visceral pain and can improve pain and reduce postoperative discomfort, thereby speeding mobilization and shortening hospital stay (Sardi et al., 2022). However, studies of pain scale and IL-6 with lidocaine and fentanyl in post-curettage patients are limited, and no study of this question in curettage was found. The present study therefore aimed to compare pain scale and IL-6 levels after general anesthesia with fentanyl or lidocaine in obstetric patients undergoing curettage.

METHODS

Research Design and Sample

This was a double-blind randomized controlled trial, with simple randomization of participants before the intervention, conducted at the Comprehensive Emergency Obstetric and Neonatal Care Unit (PONEK) of Dr. Moewardi General Hospital, Surakarta, Indonesia, from August to October 2023. The population comprised patients undergoing curettage at the hospital, and the sample consisted of all patients who met the eligibility criteria and agreed to participate, recruited by consecutive sampling until the required sample size was reached (Sastroasmoro & Ismael, 2016).

Inclusion criteria were willingness to participate, ability to communicate well in Indonesian, pregnant women aged 20–40 years, curettage for an obstetric indication, and American Society of Anesthesiologists (ASA) physical status I–II. Exclusion criteria were comorbid conditions such as hypertension, preeclampsia, diabetes mellitus, or other diseases that disturb body metabolism; hematologic or coagulation disorders or antiphospholipid syndrome; surgery lasting 60–120 minutes; and contraindications to general anesthesia. Participants were dropped out if postoperative NRS exceeded 7, if they received analgesic drugs from the operator after surgery, or if they were allergic to the study drugs.

The sample size was calculated with the formula for comparing two means, using the 12-hour postoperative NRS reported by Shadvar et al. (2017) (lidocaine 4.09 ± 1.067; fentanyl 3.11 ± 0.517), with a Type I error of 5% ($Z\alpha = 1.64$) and a Type II error of 20% ($Z\beta = 0.84$). This gave 14 participants per group, which was inflated for an expected 10% dropout to 16 per group, so 32 participants were included in total. The calculation was based on the 12-hour NRS, not on IL-6, and no non-inferiority margin was specified.

Intervention Procedure

After approval by the research ethics committee and informed consent, patients scheduled for curettage were screened against the eligibility criteria. For consenting patients, age, diagnosis, heart rate (HR), mean arterial pressure (MAP), hemoglobin, leukocyte count, and date of surgery were recorded, and patients were taught how to rate pain with the NRS. Participants were then randomized 1:1 to Group I (fentanyl) or Group II (lidocaine) (Figure 1).

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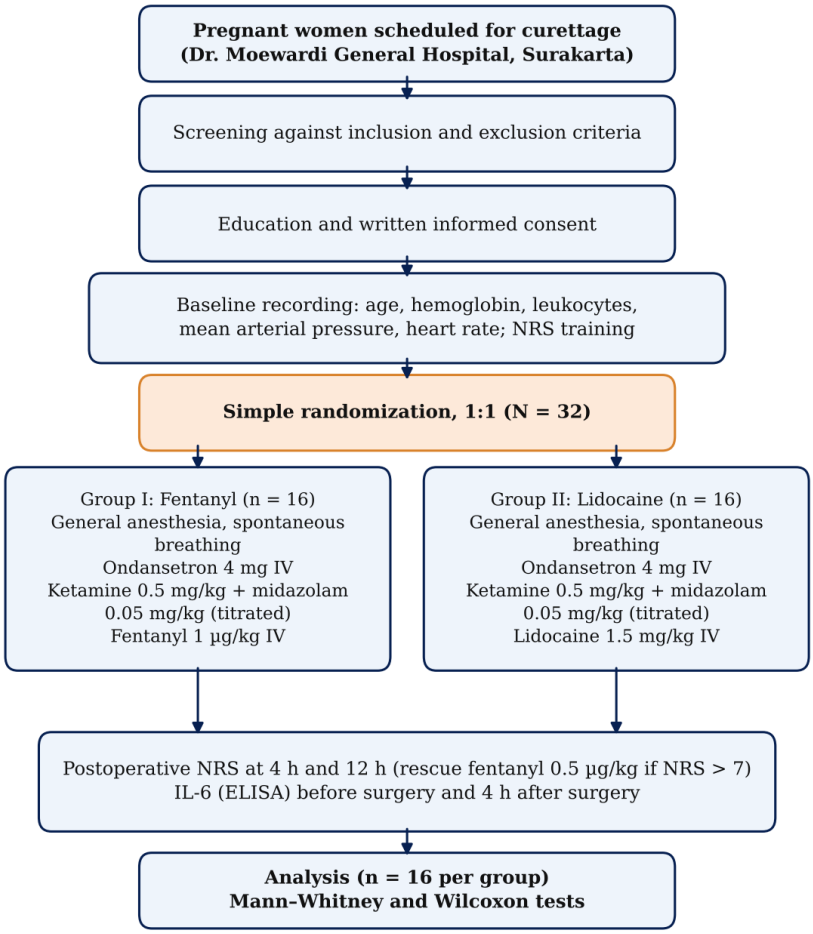


Figure 1. Study flow chart.

All procedures used general anesthesia with spontaneous breathing. Participants received ondansetron 4 mg intravenously as premedication, and anesthesia was induced with ketamine 0.5 mg/kg combined with midazolam 0.05 mg/kg, titrated until the patient fell asleep. Once the airway and ventilation were controlled, Group I received fentanyl 1 µg/kg intravenously and Group II received lidocaine 1.5 mg/kg intravenously. During surgery, blood pressure, HR, duration of surgery, and the amount of opioid and lidocaine given were monitored. If the postoperative NRS exceeded 7, fentanyl 0.5 µg/kg was given as additional analgesia.

Measures and Data Analysis

The primary outcomes were pain intensity, measured with the NRS through an interview at 4 and 12 hours after surgery, and IL-6 concentration (pg/mL), measured by enzyme-linked immunosorbent assay (ELISA) before surgery and 4 hours after surgery.

Data were analyzed with IBM SPSS version 24. Normality was assessed with the Shapiro–Wilk test because the sample was small ($n \leq 50$), with $p > .05$ indicating normal distribution. Because the outcome data were not normally distributed, differences between independent groups were tested with the Mann–Whitney test and changes within groups with the Wilcoxon signed-rank test. Baseline characteristics were compared with the independent t-test or the Mann–Whitney test, as indicated in Table 1. Statistical significance was set at $p < .05$ with a 95% confidence interval.

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RESULTS

Participant Characteristics

Thirty-two patients were analyzed, 16 in each group. Baseline characteristics are shown in Table 1. Most participants were aged 20–30 years (fentanyl group, 12 of 16, 75.0%; lidocaine group, 9 of 16, 56.3%). Age, hemoglobin, MAP, and leukocyte count did not differ significantly between the groups (all $p > .05$). Only HR differed significantly, with a higher mean in the lidocaine group (86.87 beats/min) than in the fentanyl group (79.68 beats/min; $p = .001$).

Table 1. Baseline characteristics of participants by group

Characteristic	Fentanyl (n = 16)	Lidocaine (n = 16)	p
Age (years)	26.31 ± 5.43	29.00 ± 6.87	.229[a]
Hemoglobin (g/dL)	12.38 ± 1.34	12.59 ± 0.69	.603[a]
MAP (mmHg)	93.37 ± 9.22	90.06 ± 7.96	.361[b]
Leukocytes ($\times 10^3/\mu L$)	11.50 ± 2.34	11.00 ± 1.66	.724[b]
Heart rate (beats/min)	79.68 ± 6.15	86.87 ± 4.16	.001[a]

Note. Values are mean ± SD. MAP = mean arterial pressure. [a] Independent t-test. [b] Mann–Whitney test.

Postoperative Pain

Pain scores fell significantly between 4 and 12 hours after surgery in both groups (Table 2). In the fentanyl group the mean NRS decreased from 4.000 to 2.375 (mean change −1.625), and in the lidocaine group from 4.188 to 2.625 (mean change −1.563); both changes were significant ($p < .001$). Between-group comparisons showed no significant difference in NRS at 4 hours ($p = .515$) or at 12 hours ($p = .361$), so no difference in postoperative pain was detected between intravenous lidocaine and intravenous fentanyl (Figure 2a).

Table 2. Numeric Rating Scale scores at 4 and 12 hours after surgery

Group	4 h postoperative	12 h postoperative	Change	p (within group)[a]
Fentanyl	4.000 ± 0.730	2.375 ± 0.619	−1.625 ± 0.719	< .001
Lidocaine	4.188 ± 0.655	2.625 ± 0.719	−1.563 ± 0.629	< .001
p (between groups)[b]	.515	.361		

Note. Values are mean ± SD. [a] Wilcoxon signed-rank test. [b] Mann–Whitney test.

Interleukin-6

IL-6 concentrations rose significantly in both groups from before surgery to 4 hours after surgery (Table 3). The mean increased from 8.625 to 12.650 pg/mL in the fentanyl group (change 4.025) and from 9.000 to 13.163 pg/mL in the lidocaine group (change 4.163); both increases were significant ($p < .001$). IL-6 did not differ significantly between the groups before surgery ($p = .867$) or at 4 hours after surgery ($p = .793$) (Figure 2b). The mean 4-hour IL-6 was numerically higher in the lidocaine group, but the difference was not statistically significant.

Table 3. Interleukin-6 concentrations (pg/mL) before and 4 hours after surgery

Group	Preoperative	4 h postoperative	Change	p (within group)[a]
Fentanyl	8.625 ± 3.775	12.650 ± 6.476	4.025 ± 3.442	< .001
Lidocaine	9.000 ± 4.662	13.163 ± 7.554	4.163 ± 6.880	< .001
p (between groups)[b]	.867	.793		

Note. Values are mean ± SD. [a] Wilcoxon signed-rank test. [b] Mann–Whitney test.

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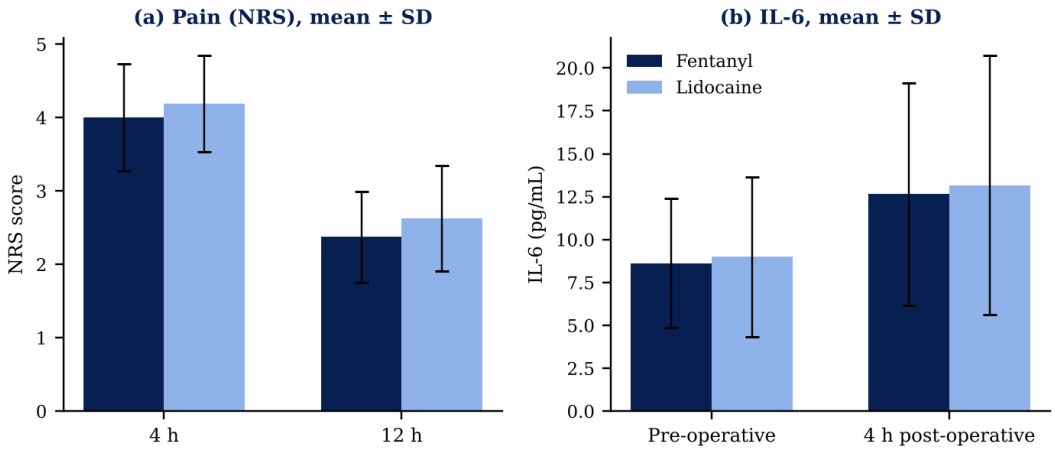


Figure 2. Mean pain scores (a) and IL-6 concentrations (b) by group. Error bars indicate SD.

DISCUSSION

Postoperative Pain

This trial found that pain scores decreased significantly in both groups from 4 to 12 hours after curettage and that pain did not differ significantly between patients given intravenous lidocaine and those given intravenous fentanyl. This is in line with earlier reports that preoperative intravenous lidocaine 1.5 mg/kg reduced pain after hysteroscopy under general anesthesia (Lee et al., 2020) and that bolus and continuous intravenous lidocaine decreased pain intensity (Sardi et al., 2022). Lidocaine is an effective modality for visceral pain and can relieve postoperative discomfort, thereby speeding mobilization and shortening hospital stay (Sardi et al., 2022).

The analgesic action of lidocaine is explained by blockade of sodium influx in nerve fibers, so that pain transduction does not occur (Talukdar et al., 2020). On binding, lidocaine induces a conformational change in the sodium channel that prevents sodium entry and therefore depolarization. Sodium channels are expressed on Aδ and C fibers, and their blockade reduces the ectopic discharge that underlies certain aspects of persistent pain (Gudin & Nalamachu, 2020). Pain is also modulated at every level of the nociceptive pathway, from the primary afferent neurons and dorsal horn to higher brain centers, through ascending and descending regulation (Aribawa et al., 2019; Yam et al., 2018), which gives drugs with different mechanisms, such as lidocaine and fentanyl, several routes to a similar clinical effect.

The mean pain scores at 12 hours were nearly identical in the lidocaine (2.625 ± 0.719) and fentanyl (2.375 ± 0.619) groups, and the between-group tests were not significant (p = .515 and p = .361). These results suggest that, at the doses used, no difference in postoperative analgesia between the two drugs was detected. Two cautions apply. First, the study had no group without analgesic, so the fall in NRS between 4 and 12 hours cannot be attributed to either drug alone, because pain naturally tends to decline as patients recover. Second, a non-significant difference in a trial with 16 participants per group, which may be underpowered, does not by itself demonstrate equivalence or non-inferiority, as no non-inferiority margin was defined in advance. The findings are therefore interpreted as showing no detectable difference, not as proof that lidocaine is non-inferior to fentanyl.

Interleukin-6 Response

IL-6 increased significantly after surgery in both groups, and the increase did not differ between fentanyl and lidocaine. Pro-inflammatory cytokines such as IL-6 rise significantly after surgical intervention and intraoperative fentanyl, with or without local anesthesia. Central sensitization is thought to be the main contributor to fentanyl-associated surgical hyperalgesia, but the up-regulation of pro-inflammatory cytokines

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suggests that peripheral mechanisms also contribute to some degree (Chang et al., 2018). Fentanyl and other opioids can attenuate the release of humoral and inflammatory mediators: exposure of human monocytes and granulocytes to fentanyl significantly reduces chemotaxis, phagocytosis, oxidative activity, and the ability of cells to respond to stimulatory molecules such as TNF-α, IL-8, and IL-6 (Amiri et al., 2014; Fekkes et al., 2016). The dose of fentanyl is a plausible reason why no suppression of IL-6 was seen. The immunosuppressive effect of fentanyl has been described in humans in a dose-related manner. In the perioperative human studies summarized by Franchi et al. (2019), fentanyl was grouped as low (2–4 μg/kg), intermediate (23–30 μg/kg), and high dose (70–100 μg/kg), and intermediate and high doses lowered IL-1 and IL-6 significantly more than low doses. The 1 μg/kg used here is below even the low-dose range of those studies and far below the doses at which suppression was observed, so low-dose fentanyl would not be expected to suppress IL-6 and could not be distinguished from lidocaine on this outcome. The same review notes that surgery is itself immunosuppressive and that cytokine measurement methods differ between studies. No group in this trial received a medium or high fentanyl dose, so this explanation was not tested.

Systemic lidocaine has antinociceptive, antiarrhythmic, anti-inflammatory, and antithrombotic effects (Karnina & Ismah, 2021). It has been associated with reduced release of pro-inflammatory cytokines, which may influence the acute-phase inflammatory reaction, and down-regulation of the cytokines that produce peripheral and central sensitization is related to less pain (Lee & Schraag, 2022). Local anesthetics also inhibit neutrophil adhesion, migration, and accumulation as well as macrophage activity (Vosoughian et al., 2021). In the present study, however, both fentanyl and lidocaine were followed by a rise in IL-6, which differs from what these mechanisms would predict.

The pattern agrees with part of the clinical literature. In women undergoing hysterectomy for ovarian neoplasm, IL-6 in the lidocaine group increased at 1 and 6 hours after incision and fell at 24 hours, which the authors linked to the mode of administration (initial bolus), the dose, the type of surgery, and the duration of lidocaine given during and after surgery, and they suggested that intravenous lidocaine be given both perioperatively and postoperatively to attenuate the stress response (Sardi et al., 2022). IL-6 was also significantly higher than baseline 2 hours after laparoscopic hysterectomy (Xu et al., 2021), and perioperative intravenous lidocaine reduced early postoperative pain, nausea, and morphine consumption within 24 hours without lowering plasma IL-6 after laparoscopic gastroplasty (de Oliveira et al., 2020). In contrast, in children undergoing spinal surgery, lidocaine reduced pain at rest and during movement for up to 6 hours, and pro-inflammatory mediators, including nerve growth factor and IL-6, were lower at 6 hours after surgery (Hall et al., 2021; Kościelniak-Merak et al., 2020).

Our design, with a single intravenous bolus at induction, a single postoperative IL-6 sample at 4 hours, and no continuous infusion, may therefore have contributed to the absence of an anti-inflammatory signal, but whether the bolus was the main reason cannot be established, because there was no infusion arm for comparison. A bolus-only regimen is nevertheless a plausible contributor: the elimination half-life of lidocaine after an intravenous bolus is typically 1.5 to 2 hours (Pfizer Inc., n.d.), so plasma concentrations would have fallen considerably by the 4-hour sample, after the inflammatory response to surgery had developed. Against treating the bolus as the main explanation, Sardi et al. (2022), who gave a bolus followed by continuous lidocaine, also found no significant IL-6 reduction, and de Oliveira et al. (2020) found none with perioperative intravenous lidocaine. Other factors may therefore also have contributed: IL-6 rises after surgical injury irrespective of the analgesic used, so a rise in both groups is expected; the timing of the peak varies between patients, and one sample at 4 hours could miss the peak or a later difference; and with 16 participants per group and large standard deviations the study had limited power to detect a modest anti-inflammatory effect. The rise was also modest in absolute terms (about 4 pg/mL in both groups), which may reflect the limited tissue trauma of curettage.

In this study, the mean 4-hour IL-6 was numerically higher in the lidocaine group (13.163 ± 7.554 pg/mL) than in the fentanyl group (12.650 ± 6.476 pg/mL), but the between-group difference was not significant (p = .793).

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The large standard deviations relative to the means show considerable individual variability, which, together with the small sample, limits the precision of these estimates.

Baseline Heart Rate Imbalance

Baseline heart rate differed between the groups (lidocaine 86.87 ± 4.16 vs fentanyl 79.68 ± 6.15 beats/min, p = .001), a difference of about 7 beats/min, although both means lie within the normal resting range. With simple randomization and 16 participants per group, such an imbalance is most likely a chance finding, and it would remain significant against a Bonferroni-adjusted threshold of .01 for the five continuous baseline variables in Table 1. A higher baseline heart rate may reflect greater preoperative anxiety or sympathetic tone, which could increase postoperative pain ratings; preoperative anxiety was not assessed. If present, this bias would disadvantage the lidocaine group. The lidocaine group did have numerically higher NRS scores (4.188 vs 4.000 at 4 hours and 2.625 vs 2.375 at 12 hours), but the differences were small and not significant, so the absence of a between-group difference does not appear to be produced by the heart rate imbalance. No covariate adjustment was performed for baseline heart rate. Future trials should use stratified or block randomization and adjust the analysis for baseline heart rate.

CONCLUSION AND IMPLICATIONS

In obstetric patients undergoing curettage under general anesthesia, intravenous lidocaine 1.5 mg/kg and intravenous fentanyl 1 µg/kg showed no detectable difference in NRS pain scores at 4 and 12 hours or in IL-6 concentrations before and 4 hours after surgery. Pain decreased and IL-6 increased significantly in both groups. Because the study was small, possibly underpowered, and had no prespecified equivalence or non-inferiority margin, these findings show no detectable difference and do not prove that lidocaine is non-inferior to fentanyl.

Clinical Recommendations

These findings support considering intravenous lidocaine 1.5 mg/kg, given after induction, as an opioid-free intraoperative analgesic option for short outpatient curettage under general anesthesia, particularly in resource-limited settings or where opioids are restricted or unavailable. Because lidocaine produced pain scores similar to fentanyl with no detectable difference, it can be used when fentanyl is not obtainable but should not routinely replace fentanyl until adequately powered trials with a prespecified margin confirm the finding. A mean NRS of about 4 at 4 hours in both groups corresponds to moderate pain, so multimodal postoperative analgesia is advisable whichever intraoperative drug is used.

Limitations and Future Research

This study has several limitations. The sample was small and came from a single center, and the study may be underpowered, particularly for IL-6, because the sample size was calculated from the 12-hour NRS. There was no non-inferiority margin and no group without analgesic, so equivalence and the absolute effect of each drug could not be established. The groups differed in baseline heart rate, and no adjustment for it was made. Lidocaine was given only as a single bolus, without continued intraoperative or postoperative infusion, and preoperative anxiety was not assessed. IL-6 was measured at only two time points.

Future studies should use larger, preferably multicenter, samples with a prespecified non-inferiority margin, stratified or block randomization with adjustment for baseline heart rate, a lidocaine infusion arm that continues after surgery, a group receiving medium-dose fentanyl, and IL-6 measurement at several later time points, and should assess preoperative anxiety.

DECLARATIONS

Ethics approval: The study was approved by the health research ethics committee of the Faculty of Medicine, Universitas Sebelas Maret, and Dr. Moewardi General Hospital.

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Author contributions: Restian Rudy O.: conceptualization, methodology, investigation, data curation, formal analysis, writing – original draft. Rth. Supraptomo: supervision, methodology, writing – review and editing. Purwoko: supervision, methodology, writing – review and editing. Septian Adi Permana: validation, writing – review and editing. Fitri Hapsari Dewi: project administration, validation, writing – review and editing. All authors have read and approved the final manuscript.

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